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B. Kenny
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Philip C. Comp

Serial No.: 08/323,060 Art Unit: 1806

Filed: October 14, 1994 Examiner: R. Schwadron

For: BLOCKAGE OF PROTEIN C ACTIVATION REDUCES MICROVASCULAR SURGICAL BLOOD LOSS

Assistant Commissioner for Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1-9, 11-16, and 19-21 in the Office Action mailed November 27, 1995, maintained in the Advisory Action mailed March 27, 1996, in the above-identified patent application. A Notice of Appeal was mailed on April 29, 1996. A Petition for an extension of time for one month, up to and including July 29, 1996, and the appropriate fee accompany this Appeal Brief. A check in the amount of $145.00 for filing of the Appellant's Brief is also enclosed.

(1) REAL PARTY IN INTEREST

The real party in interest is the Oklahoma Medical Research Foundation, a non-profit Oklahoma corporation, the assignee of this application.

(2) RELATED APPEALS AND INTERFERENCES

No other related appeals or interferences are known to Appellant, the undersigned, or Appellant's assignees that directly affect, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 1-9, 11-16 and 19-21 in the above-identified application, as amended by the Amendment mailed February 27, 1996, stand rejected under 35 U.S.C. § 103 and § 112, first and second paragraphs. The text of the pending claims on appeal is set forth in the Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

An Office Action was mailed from the U.S. Patent Office on November 27, 1995, in which claims 1-9, 11-16, and 19-21 were finally rejected. An Amendment was mailed on February 27, 1996. The Examiner mailed an Advisory Action on March 27, 1996, indicating that the Amendment mailed February 27, 1996, would be entered upon filing of an appeal.

(5) SUMMARY OF THE INVENTION

The present invention is directed to methods and compositions for reducing blood loss from microvascular bleeding due to wounds caused by surgery or trauma. The methods and

compositions are particularly useful in treating microvascular bleeding from skin graft donor sites, burns, bleeding liver surfaces, and inflamed visceral surfaces.

The claimed compositions have two components: the first is an inhibitor of one or more natural anticoagulants: protein C, thrombomodulin, antithrombin II, heparin cofactor II and tissue factor pathway inhibitor, which is in a carrier for systemic administration; and the second is a coagulant in a pharmaceutically acceptable carrier for topical administration.

The claimed method is based on the administration of an inhibitor of greater than 90% of one or more natural anticoagulants: protein C, thrombomodulin, antithrombin II, heparin cofactor II and tissue factor pathway inhibitor, in an amount effective to prevent anticoagulation. Experiments demonstrated that Appellant's method and composition were as effective as the standard treatment of applying topical agents such as thrombin or tissue thromboplastin. However, Appellant's invention is more advantageous because topical administration is not always feasible. Additionally, Appellant discovered that the combined systemic administration of an inhibitor of the natural anticoagulant, protein C (HPC4 antibody) with topical administration of thrombin synergistically reduced microvascular blood loss even further.

(6) ISSUES ON APPEAL

The issues presented on appeal are as follows:

(a) Whether claims 1-9, 11-16, and 19-21 were properly rejected under 35 U.S.C. § 112, first and second paragraphs, as not enabled and indefinite;

(b) Whether claims 1-9, 11-16, and 19-21 should be rejected under 35 U.S.C. § 103 as obvious over U.S. Patent No. 5,202,253 to Esmon *et al.*, alone, or in view of U.S. Patent No. 5,130,244 to Nishimaki *et al.*, or in view of Furie *et al.*, *Cell* 53, 505-518 (1988).

(7) GROUPING OF CLAIMS

Appellant submits that claims 1-9, 11-16, and 19-21 do not stand or fall together. Claim 1 is an independent, generic method claim, requiring administration of an inhibitor of at least 90% of a natural anticoagulant selected from the group consisting of protein C, thrombomodulin, antithrombin II, heparin cofactor II and tissue factor pathway inhibitor. The dependent claims are drawn to use of a protein C inhibitor (claim 2), specifically a monoclonal antibody immunoreactive with protein C (claim 20), even more specifically HPC-4 as deposited with the ATCC (claims 21), systemic administration of the inhibitor (claim 3), topical administration of the inhibitor (claim 4), administration of the inhibitor in combination with topical administration of a coagulant (claims 5, 8, and 19), where the coagulant is either thrombin or tissue thromboplastin (claim 6) and in a defined dosage (claim 9). Dependent claims 11-13 are defined by the class of patient to be treated: where the patient is a burn patient (claim 11), a patient with skin or tissue grafts (claim 12), or a patient with cerebral contussions (claim 13).

Claim 14 is an independent composition claim requiring two components: the first, in a carrier for systemic administration, an inhibitor of a natural anticoagulant, and the second, a coagulant in a carrier for topical administration. Dependent claim 15 defines the inhibitor

as an inhibitor of protein C; claim 16 defines the coagulant as either thrombin or thromboplastin.

(8) ARGUMENTS

(a) Background of the Invention.

Appellant, Dr. Comp, is a medical doctor and researcher in the field of blood clotting disorders and the components involved in this process. In the late 1980's, he and Dr. Charles Esmon discovered that an inhibitor of a natural anticoagulant, protein C, could be used to kill tumors. They used a monoclonal antibody immunoreactive to protein C, but not the "activated" form of protein C, referred to as HPC-4, in their studies in a variety of animal species having a number of different solid tumors to demonstrate efficacy. This discovery formed the basis of a patent application which issued with claims to methods and compositions for inhibition of tumors in 1992 as U.S. Patent No. 5,147,638 to Charles Esmon and Philip Comp. An earlier filed application issued with claims to the HPC-4 antibody in 1993 as U.S. Patent No. 5,202,253 to Charles and Naomi Esmon.

The method for treating tumors was enhanced by the use of a cytokine, such as tumor necrosis factor, and was thought to kill the tumors by causing massive microvascular clotting within the tumors but not in normal tissue. It was not known why the systemic or local administration of the inhibitor, alone or in combination with a cytokine, did not cause clotting to occur in tissues other than the tumors, however, extensive autopsies showed the results were consistent in all animal models tested, including dogs, cats, pigs, and baboon.

Dr. Comp subsequently determined that systemic administration of an inhibitor of a natural anticoagulant, such as protein C, could also be used to inhibit microvascular bleeding in normal patients. This is typical of injuries such as in burn and skin graft patients, where large areas "ooze" fluids, causing extensive fluid loss, and pain due to adhesion to bandages, as well as serving as entry sites for infection. It also occurs in brain trauma patients, where it is extremely difficult to treat without the risk of a clot forming and causing a stroke.

Dr. Comp conducted his experiments in pigs, removing areas of skin grafts (0.015 inches in thickness, application page 17). He treated the injured tissue with either (1) systemic HPC4; (2) systemic HPC4 with topical thrombin; (3) systemic HPC4 with topical thromboplastin; (4) saline control; (5) topical thrombin (prior art treatment); topical thromboplastinc (application page 18). The analysis of the various treatments showed that systemic HPC4 was generally equivalent to the results obtained with topical throbmin or tissue thromboplastin, demonstrating the efficacy of systemic treatment of microvascular bleeding using an inhibitor of a natural anticoagulant. The analysis also demonstrated that the combination of systemic inhibitor with topical coagulant achieved a **33 to 44% decrease in blood loss** ($p < 0.05$) as compared with either systemic administration of inhibitor alone or topical thrombin alone (page 20, Figures 2 and 3).

(b) Claims 1-9, 11-16, and 19-21 are enabled under 35 U.S.C. § 112, first paragraph.

The specification was objected to and claims 1-9, 11-16 and 19-21 rejected under 35 U.S.C. § 112, first paragraph, on the basis that the specification fails to provide an adequate written description of the invention and fails to adequately teach how to make and/or use the invention. These objections and rejections are without support.

The requirement under 35 U.S.C. §112 is that applicant must provide a written description of how to make and use the claimed invention, i.e., a method of inhibiting microvascular bleeding such as exists at the surface of a burn wound, and a composition for administration to a patient of an inhibitor of a natural anticoagulant in a carrier for systemic administration in combination with a topical coagulant.

The rejections were made on the following basis:

(a) that pigs are not predictive of humans;

(b) lack of guidance of dosage and time of administration of a topical inhibitor of a natural anticoagulant;

(c) the application is only enabling for the use of HPC-4 antibody in pigs;

(d) the application is only enabling where the HPC-4 antibody is given prior to the initiation of the microvascular blooding.

The Examiner erroneously asserts that Appellant's claimed method would require undue experimentation, that pigs are not predictive of efficacy in humans, and that HPC4 is not predictive of other inhibitors of natural anticoagulants. These assertions are made

without an adequate basis to establish a *prima facie* case of lack of enablement. Moreover, even if a prima facie case of non-enablement had been established, Appellant has clearly provided evidence to rebut a *prima facie* case of lack of enablement.

i. The application provides detailed methods and materials, and examples showing actual reduction to practice of the claimed method and compositions.

In response, the Board's attention is drawn again to the application as originally filed. Pages 6-14 provide a clear description of the inhibitors of the natural anticoagulants defined by the independent claims; page 13 describes the topical coagulants that are available. Pharmaceutically acceptable carriers are described at page 14, lines 17-20. The effective dosage of an inhibitor of a natural anticoagulant is described at page 14, lines 21-27, and page 15, line 29 to page 16, line 24. The effective dosage of the topical coagulant is described at page 16, lines 25-31. Topical coagulants and effective dosages are also well known to those skilled in the art; see, for example, Furie, *et al.*, 53 *Cell* 505-18 (1988); Suzuki, *et al.*, 53 *Thrombosis Res.* 271-77 (1989); and U.S. Patent No. 5,130,244. Pages 13 to 14 describe the disorders that can be treated. The examples at pages 17 to 21 demonstrates reduction to practice and efficacy of the claimed composition using pigs as an animal model and even go so far as to provide multiple comparisons with prior art compositions and statistical analysis of the results.

With regard to the order of administration, the Board should understand that one of the problems with microvascular bleeding is that there is ongoing generation of activated

protein C; it is not just all activated in a matter of seconds and then no more is generated. This is in fact one of the major reasons it is difficult to stop. Accordingly, there is no reason the claims should be limited to administration before bleeding has begun - which is also rather impractical since one rarely presents for treatment **prior** to injury!

Although the Examiner seems to be concerned regarding the possibility of pathologic thrombosis whenever a systemic thrombogenic drug is utilized, no evidence has been provided that one would expect such a condition to occur. Applicant is an M.D. who is actively treating patients, as well as a researcher, as is Dr. Fass, who's declaration is discussed below. The consideration of pathologic thrombosis in the application relates to abnormalities associated with congenital deficiencies in protein C, not from the transient inhibition of protein C, as described at page 14, last paragraph. Page 15, lines 29-33 state that titration of the dosage is possible so that inactivation of a specific fraction of the circulating protein C pool is achieved. Dosage titration is well known in the art. Page 16, lines 12-16, describes how normal protein C activity can be reestablished by administering extrinsic "pre"-activated protein C. One skilled in the art could apply one of these procedures for use in conjunction with use of any of the claimed agents if so desired.

ii. The appellant has provided numerous literature and scientific support for the predictability of the materials used in the examples for the efficacy of the claimed materials.

The appellant has provided numerous publications and literature support for the predictability of the treatment of pig skin grafts with an inhibitor of protein C, HPC4, and

commercially available thrombin and tissue thromboplastin, for the broad class of claimed inhibitors and topical coagulants, and for the more specific issue of the clinical utility of an animal monoclonal antibody in the claimed method. For example, attached to the Amendment mailed August 2, 1993, were several publications showing efficacy of HPC4 in other animal species (Taylor, et al., *J. Clin. Invest.* 79, 918-925 (1987) and Taylor, et al., *J. Trauma* 30, 5197-5203 (1990), showing efficacy of HPC4 in blocking the protective effect of protein C in gram negative septicemia); Taylor, et al., *Blood* 78(2), 357-363 (1991), showing similar results obtained using inhibitors of protein S and C4bBP as for an inhibitor or protein C in the baboon model; Broze, *Seminars in Hematology* (1992), for a general review of the coagulation pathway, and Montagna and Yun, *J. Investigative Dermatology* 43, 11-22 (1964) for a discussion of pig skin.

Attached to the Amendment mailed August 17, 1995, were copies of U.S. Patent No. 5,147,638 to Esmon, et al., with examples at col. 11-17 showing efficacy of a protein C inhibitor, HPC4, in inhibiting tumor growth in dogs and pigs; Genetic Engineering News (October 1, 1994) reporting the results of clinical trials using mouse monoclonal antibodies in humans for treatment of gram negative sepsis and UHC Biotechnology Monitor (January 1994) reporting clinical studies using mouse and other animal monoclonal antibodies for systemic treatment of cancer, multiple sclerosis, and imaging. Also enclosed was a product brochure for oncoscint CR/OV™, a tumor targeted cancer detection murine monoclonal antibody, a product brochure for Digibind™, a murine monoclonal for imaging, a fact sheet for NeoRx, a company marking monoclonal antibodies as cancer imaging agents, and an

article by Petersen, et al., *Amer. J. Surg.* 165, 137-143 (1993), on the use of a radiolabeled murine monoclonal antibody in the management of colon cancer in humans.

iii. The appellant has provided an independent, uncompensated, expert opinion that the claims are enabled and non-obvious to one skilled in the art.

When all of the foregoing was still considered insufficient by the Examiner, the undersigned and appellant conducted a telephone interview with the Examiner. During the interview, the Examiner indicated that he would consider an independent expert opinion in determining the enablement and non-obviousness of the claimed method and compositions. The appellant contacted Dr. David Fass, an acknowledged expert in the field of coagulation, especially in comparisons of the porcine and human coagulation systems. Dr. Fass is a researcher in Hematology at the Mayo Clinic in Rochester, Minneapolis. He has conducted research in the area blood coagulation for over twenty years (Declaration, paragraph 1). Dr. Fass was provided with a copy of the patent application, the Office Action mailed November 27, 1995, and the publications cited therein (Declaration, paragraph 2). Dr. Fass was not compensated for his time.

Dr. Fass first notes that there are many variations in skin characteristics, depending on the species, the ethnic background of the individual, the age of the individual, and the location on the body; then states that this is not relevant to the claimed subject matter. What is relevant is the predictability of results obtained in the porcine coagulation system relative to the predictability of results obtained in the human coagulation system; concluding that the

pig coagulation system is an extremely good model for the human coagulation system, probably better than some species of primates (Declaration, paragraphs 3, 4, and 5). Dr. Fass then discusses the Waldmann paper cited by the Examiner in support of his position that one cannot treat humans with murine monoclonal antibodies, concluding that Waldman is only one person's opinion, unsupported by data, and not consistent with the clinical evidence (Declaration, paragraphs 7 and 8). Dr. Fass concludes that the claimed method and compositions are not obvious from the cited publications, and that the Examiner's conclusion stems from a basis misunderstanding of the clotting mechanisms that are involved, and that the examples support for the breadth of the claimed methods and reagents (Declaration, paragraph 9).

iv. The Examiner Erred in Refusing to Consider the Declaration under 37 C.F.R. § 1.132 of Dr. Fass.

In the Advisory Action mailed March 27, 1996, the Examiner refused to consider the declaration of Dr. Fass on the basis that "applicant has not shown good and sufficient reasons why it was not earlier presented. In addition, the Fass declaration supplied with the amendment filed 2/29/96 was not signed" (p. 2, ¶ 6).

The Declaration of Dr. Fass was mailed on February 27, 1996, with an Amendment under 37 C.F.R. §1.116, in response to a telephone interview conducted on December 12, 1995, just before the Christmas holidays. The materials required for Dr. Fass to review were provided in mid-January, 1996. Dr. Fass provided his draft declaration in mid-February, 1996. Dr. Fass was unavailable during the time the unexecuted Declaration was

mailed to the U.S. Patent Office. After returning to Rochester, Dr. Fass executed the Declaration and returned it to the undersigned for filing in the Patent Office. On March 28, 1996, Appellant mailed the *executed* Declaration under §1.132, signed by Dr. Fass on March 18, 1996, to substitute for the *unexecuted* declaration filed earlier.

Pursuant to 37 C.F.R. § 1.132, applicant is entitled to submit declarations traversing rejections or objections, *inter alias*, on reference to a domestic patent. Appellant's application was rejected over U.S. Patent No. 5,202,253 to Esmon *et al.*, and other domestic patents. Furthermore, "all affidavits or declarations presented which do not fall within or under other specific rules are to be treated or considered as falling under this rule." MPEP § 716. It is proper to consider affidavits presenting opinions of experts skilled in the relevant art. *In re Oelrich*, 579 F.2d 86, 198 U.S.P.Q. 210 (C.C.P.A. 1978). Dr. Fass is a distinguished expert in the field of blood coagulation in both pigs and humans, the subject of Appellant's invention. For these reasons, the submission of the declaration of Dr. Fass under 37 C.F.R. § 1.132 was clearly proper.

MPEP § 716 also states that "an affidavit or declaration presented with a first response after final rejection for the purpose of overcoming a new ground of rejection or requirement made in the final rejection is entered and considered **without** a showing under 37 C.F.R. 1.116(b)" (emphasis added). The declaration of Dr. Fass was properly submitted with a first response following final rejection, and responded to issues raised by the Examiner **after**the final rejection, during the telephone interview. The interview would not

have been granted after final rejection merely to "restate arguments of record." *See* MPEP § 713.09.

In the telephone interview, the Examiner indicated that Appellant should submit expert testimony of a third party to establish that (1) the porcine model is predictive to one of ordinary skill in the art, (2) HPC4 is predictive of other inhibitors, and (3) one could typically expect animal antibodies to work in Appellant's claimed compositions and methods. The declaration of Dr. Fass provides this testimony, supporting the enablement and non-obviousness of Appellant's claims. Because the declaration was responsive to matters raised by the Examiner *after* the final rejection was made, Appellant should not be required under 37 C.F.R. § 1.116(b) to have shown good and sufficient reasons why the declaration was not earlier presented. As is clear from the foregoing discussion, appellant had twice submitted evidence that should have been sufficient to respond to the issues previously raised by the examiner. It was only during the telephone interview that it became apparent that the Examiner's refusal to give weight to the publications and examples was due to his desire to obtain an independent, expert opinion regarding the merits of appellant's arguments.

It was erroneous and unreasonable for the Examiner to refuse to consider the declaration of Dr. Fass, especially after the declaration was obtained at his request!

The declaration was written and reviewed by Dr. Fass. An unexecuted copy was submitted with the amendment mailed February 27, 1996, because Dr. Fass was unavailable to sign it. However, an executed copy was submitted as soon as possible, within days after obtaining Dr. Fass's signature and within 30 days of mailing the amendment. This minimal

delay is not a proper basis for the Examiner's refusal to enter and consider the declaration of Dr. Fass.

Accordingly, Appellant submits that the Examiner clearly erred in not entering and considering the Declaration under 37 C.F.R. § 1.132 of Dr. David Fass.

v. The Examiner erred regarding the need for deposit of HPC4.

Claim 21 was rejected on the basis that appellant had not proven the continued availability of the claimed antibody. However, this antibody is the subject of an issued U.S. Patent, which was referenced in the application as originally filed at page 12, lines 11-19, as amended on August 2, 1993 after issuance of the patent. It is well established that the availability of a claimed antibody must be established prior to issuance of a patent. Moreover, with regard to the ongoing availability of the HPC4 antibody, the Board's attention is drawn to *In re Argoudelis* 434 F.2d. 1390 (C.C.P.A. 1970), where the Court states at page 1394:

> (1) There is always the possibility that sometime after the issuance of a patent, the disclosure which was initially enabling may become 'unenabling' and (2) whether a given disclosure which identifies a material to be employed in the practice of the claimed invention is 'enabling' within the meaning of 35 U.S.C. 112, . . . the court concluded that the possibility that at a future date one skilled in the art might no longer be enabled to practice the invention was too speculative to justify a holding that the disclosure was insufficient under § 112. (*In re Metcalfe*, 410 F.2d 1378, 56 C.C.P.A. 1191 (1969)) . . . Applying the same considerations in the present case, we note that (1) a public depository was used; . . . (3) the depository is under a contractual obligation to place the culture in the permanent collection , to supply samples to person legally entitled . . . We conclude that the possibility that the disclosure may someday become non-enabling is even more speculative than in Metcalfe, and hence does not render the disclosure insufficient under § 112.

vi. Summary.

Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The test of enablement is whether one skilled in the art could make or use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); *In re Stephens,* 529 F.2d 1343, 199 USPQ 659 (CCPA 1976). A patent need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent, Inc.,* 827 F.2d 1524, 3 USPQ2d 1737 (Fed. Cir. 1987). Determining enablement is a question of law based on underlying factual findings. *In re Vaeck,* 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); *Atlas Powder Co. v. E.I. duPont de Nemours & Co.,* 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt,* 537 F.2d 498, 190 USPQ 214 (CCPA 1976). The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required.

In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright,* 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993) (examiner must provide a

reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. As stated by the court in *In re Marzocchi,* 439 F.2d 220, 169 USPQ 367 (CCPA 1971), "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Once the examiner has established a reasonable basis to question the enablement provided for the claimed invention, the burden falls on applicant to present persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would be able to make and use the claimed invention using the disclosure as a guide. *In re Brandstadter,* 484 F.2d 1395, 179 USPQ 286 (CCPA 1973). In making the determination of enablement, the examiner shall consider the original disclosure and all evidence in the record, weighing evidence that supports enablement against evidence that the specification is not enabling. Appellant may submit factual affidavits under 37 CFR 1.132 or cite references to show what one skilled in the art knew at the time of filing the application. (MPEP §2164.05).

The application provides details as to the claimed methods and reagents, and shows actual reduction to practice and comparisons with the prior art. As demonstrated by the declaration of Dr. Fass and numerous publications submitted to the Examiner, pigs are an acceptable animal model for coagulation in humans in general, and microvascular bleeding in particular. Moreover, coagulation is not an "unpredictable art" *per se*, although as discussed below the claimed method and compositions were not obvious. These comments are equally applicable to the speculation regarding other agents with well known anticoagulant inhibitory activity (p. 4, Office Action mailed November 27, 1995). Mere assertions are not sufficient to rebut objective evidence submitted by an applicant in response to a rejection under §112.

The Examiner's argument regarding the use of animal antibodies, based on the opinion of a single author, who has not been authenticated as an expert, is contrary to what those skilled in the art believe. Not only are a number of animal antibodies in clinical use as well as clinical trials, no objective evidence has been submitted by the Examiner to support the proposition that a single use, as will generally be useful in the claimed method, would elicit any kind of problem.

Dr. Fass is clearly "one skilled in the art". His Declaration, which was uncoached and uncompensated, unequivocally states that he could practice the claimed method and composition based on the application. The examples demonstrate actual reduction to practice. The Examiner has provided no basis for rebutting the applicant's statements in the application as to the methods of use.

Accordingly, even if the Examiner had established a *prima facie* case of non-enablement, appellant has established that the claimed method and compositions are enabled.

(c) Claims 1-9, 11-16, and 19-21 are definite.

Claims 14-16 defines a composition having two components: an inhibitor of a specific natural anticoagulant in a pharmaceutically acceptable carrier for systemic administration and a coagulant for topical administration. The claims are intended to encompass two components whether in a single container or in two containers. This is not indefinite. There is a rule of common sense in reading claims - the standard is whether they are indefinite to one of ordinary skill in the art - not whether they can be twisted and misinterpreted to cover any conceivable embodiment that might not work.

The same arguments apply to the term "prevent anticoagulation" in claim 1. The claims are directed to inhibitors of named anticoagulants: protein C, antithrombin III, heparin cofactor II, thrombomodulin, and tissue factor pathway inhibitor. An inhibitor is defined in the specification and in the claim as effective to prevent anticoagulation by greater than 90% of the natural anticoagulant. Since the amount of anticoagulant normally present is known, this enables one to administer enough inhibitor to block the activity of greater than 90% of the anticoagulant.

(d) Rejections Under 35 U.S.C. § 103

Claims 1-3, 7, 11-13, and 20-21 were rejected under 35 U.S.C. § 103 as obvious over U.S. Patent No. 5,202,253 to Esmon *et al.* Claim 4 was rejected under §103 as obvious over Esmon *et al.*, in combination with U.S. Patent No. 5,130,244 to Nishimaki, *et*

al. Claims 5, 6, 8, 9, 14-16, and 19 were rejected under §103 as obvious over Esmon, *et al*, in combination with Nishimaki, *et al.*, and Furie, et al., *Cell* 53, 505-518 (1988).

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967); *In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *In re Dow Chem. Co.* 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). Appellants submit that the Examiner failed to establish a *prima facie* case of obviousness, as detailed below.

(i) The cited art.

U.S. Patent No. 5,202,253 to Esmon *et al.*

Esmon, et al. discloses and claims an antibody immunoreactive with protein C. There is no disclosure of using the antibody to inhibit microvascular bleeding. Instead, the disclosure clearly indicates that the antibody is useful for **normalization** of bleeding and clotting. The antibody is also useful to isolate protein C, and to increase the severity of gram negative sepsis (thereby demonstrating that administration of protein C may be beneficial in treating gram negative sepsis).

There is no disclosure that an inhibitor of protein C would be as effective as a coagulant such as thrombin or tissue thromboplastin in stopping microvascular bleeding if

administered systemically. A coagulant such as thrombin cannot be administered systemically - it could result in a patient developing clots throughout their body. No where is there any teaching that would lead one to expect that a systemically administered anticoagulant inhibitor could achieve clotting only in an injured area, where the bleeding is occurring. This is what is required, however, at a minimum, to make the method of claim 1 obvious. Even more is required for the combination claims. There must be some disclosure of administration of a topical coagulant to inhibit microvascular bleeding, a disclosure that systemic administration of an inhibitor of an anticoagulant could be useful, and then something that would lead one of ordinary skill in the art to expect a greater than 30% decrease in bleeding as a result of the combination! This simply cannot be achieved from Esmon, et al.

U.S. Patent No. 5,130,244 to Nishimaki *et al.*

Nishimaki, et al., merely discloses a sugar stabilized aqueous thrombin preparation. There is nothing regarding using the topically applied preparation in combination with anything else, much less a systemically administered anti-natural anticoagulant.

Nishimaki, et al., must also teach away from what is claimed since it acknowledges that the topical coagulant cannot be administered systemically; yet appellant is able to, and has claimed, systemic administration of an inhibitor of an anticoagulant.

The "obvious" combination of Esmon and Nishimaki, et al., would appear to be a topical combination of HPC4 and thrombin - since one would expect the same problems for

administration of HPC4 systemically as for thrombin, i.e., clotting throughout the patient, leading to potentially life threatening complications.

Furie, *et al.*

Furie et al. reviews the coagulation cascade. There is nothing regarding combining a topically applied coagulant preparation in combination with anything else, much less a systemically administered anti- natural anticoagulant. In fact, the authors conclude with the statement regarding the complexity of the clotting system and the interaction of soluble components with cell bound components.

(ii) The legal requirements under 35 U.S.C. §103 have not been met.

The prior art and the claimed method and compositions are discussed above.

The requirement under §103 is that the prior art must disclose each claimed element as well as provide the motivation to combine as applicant has done, with the expectation of achieving the desired result. Even assuming that there is a disclosure of each of the claimed elements of the composition in the prior art, there is simply no motivation in the cited art to combine them as defined by claims 14-16. There is no disclosure in the prior art of treating anyone by systemic administration to promote microvascular bleeding of a normal person (as compared with tumors). In fact, as demonstrated by the Declaration of Dr. Fass, the numerous publications submitted by applicant, and the '638 patent to Esmon, *et al.*, the prior art **teaches away from** applicant's claimed method and composition.

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d

686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). Here, the prior art does not disclose any method for systemic treatment of microvascular bleeding, much less that one should combine systemic with topical treatment or compositions for inhibition of microvascular bleeding.

Appellant has demonstrated the Examiner's failure to establish a *prima facie* case that the prior art suggests the claimed invention, or that the prior art indicates that the invention would have a reasonable likelihood of success. "[T]o establish a *prima facie* case of obviousness, it is necessary for the Examiner to present *evidence*, preferably in the form of some teaching, suggestion, incentive or inference in the applied prior art . . . ." *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1301 (Bd. Pat. App. & Int'f 1993). The sole basis for maintaining the rejections is, apparently, the repeated, unsupported allegation that "it would be obvious".

It is well established that "obviousness cannot be established by combining the teachings of the prior art to produced the claimed invention, absent some teaching, suggestion or incentive supporting the combination." *In re Bond* 910 F.2d 831, 834, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990) (citing *Carella v. Starlight Archery & Pro Line Co.*, 804

F.2d 135, 140, 231 U.S.P.Q. 644, 647 (Fed. Cir. 1986)); *see also ACS Hosp. Sys., Inc. v. Montefiore Hosp.* 732 F.2d 1572, 1577, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984). The Patent Office has the burden under § 103 to establish a *prima facie* case of obviousness, which can be satisfied only by showing some objective teaching in the prior art would lead one to combine the relevant teachings of the references. *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988).

The Patent Office has failed to meet this burden. "Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). TThe prior art simply does not provide the motivation to combine the systemic administration of an inhibitor of an anticoagulant with a topically applied coagulant, much less those compositions claimed for the claimed class of patients.

"One cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). Hindsight reconstruction is the only way in which the Examiner could arrive at a finding of obviousness of the claimed method in view of the cited art. The Examiner failed to identify where in the art each claimed element is shown other than to

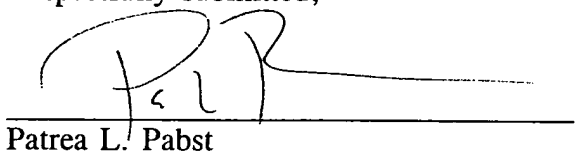
generalize that the claimed elements must be there somewhere, encompassed by what is shown. The Examiner failed to point out where the art identifies the problem to be solved or the motivation to modify and combine the disclosed processes as appellant has done. In short, the Examiner has failed to make even a *prima facie* case of obviousness of the claimed method and compositions in view of the cited art.

(9) SUMMARY AND CONCLUSION

Appellant has demonstrated that claims 1-9, 11-16, and 19-21 are clear and definite in its metes and bounds, and that the methods and compositions of claims 1-9, 11-16, and 19-21 are not obvious from any of the art of record. Appellant asserts that these rejections have been applied to the claims in error, and that the Examiner erred in refusing to consider the declaration of Dr. Fass.

For the foregoing reasons, Appellant submit that the claims 1-9, 11-16, and 19-21 should be allowed.

Respectfully submitted,



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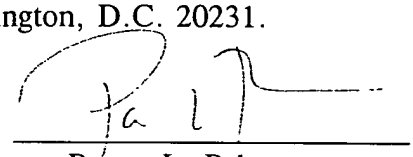

Patrea L. Pabst

Date: July 29, 1996

Appendix
Claims as Pending

1. A method for inhibiting microvascular bleeding at a site in a patient exhibiting microvascular bleeding comprising administering to the patient a compound in a pharmaceutically acceptable carrier in an effective amount to prevent anticoagulation by greater than 90% of activated protein C in human plasma, wherein the compound is an inhibitor of an anticoagulant selected from the group consisting of protein C, antithrombin III, heparin cofactor II, thrombomodulin and tissue factor pathway inhibitor.

2. The method of claim 1 wherein the anticoagulant is protein C.

3. The method of claim 1 wherein the inhibitor is administered systemically.

4. The method of claim 1 wherein the inhibitor is administered topically.

5. The method of claim 1 further comprising topically administering at the site of the bleeding a coagulant.

6. The method of claim 5 wherein the coagulant is selected from the group consisting of thrombin and tissue thromboplastin.

7. The method of claim 2 wherein the inhibitor is an antibody to protein C.

8. The method of claim 7 wherein the inhibitor is administered systemically further comprising the step of topically administering a coagulant at the site of bleeding.

9. The method of claim 8 wherein the topically administered coagulant is selected from the group consisting of thrombin in a dosage of between approximately 1000 and 10,000 units and tissue factor in a dosage of between approximately 0.1 and 10 mg.

11. The method of claim 1 wherein the inhibitor is administered to a burn patient.

12. The method of claim 1 wherein the inhibitor is administered to a patient with tissue or skin grafts.

13. The method of claim 1 wherein the inhibitor is administered to a patient with cerebral contusions.

14. A composition for inhibition of microvascular bleeding comprising as a first component an inhibitor of a natural anticoagulant selected from the group consisting of

protein C, thrombomodulin, antithrombin III, heparin cofactor II and tissue factor pathway inhibitor in a pharmaceutically acceptable carrier for systemic administration to a patient and as a second component a coagulant in a pharmaceutically acceptable carrier for topical administration to a patient.

15. The composition of claim 14 wherein the inhibitor specifically inhibits protein C.

16. The composition of claim 14 wherein the coagulant is selected from the group consisting of thrombin and tissue thromboplastin.

19. The method of claim 4 further comprising the step of topically administering a coagulant at the site of bleeding.

20. The method of claim 3 wherein the inhibitor is a monoclonal antibody immunoreactive with protein C and blocking protein C activation.

21. The method of claim 20 wherein the inhibitor is HPC-4, deposited with the American Type Culture Collection, Rockville, MD and assigned ATCC No. 9892.

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